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Tyler M. Moore, Tyler M. Moore, Elina Visoki, Stirling T. Argabright ...+9 more authors

Institutions: University of Pennsylvania, Children's Hospital of Philadelphia, University of Cambridge, Yale University ...+1 more institutions

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The Exposome and its Associations with Broad Mental and Physical Health Measures in Early Adolescence

Tyler M. Moore [a,b], Elina Visoki [b], Stirling T. Argabright [b], Grace E. DiDomenico [b], Ingrid Sotelo [b], Jeremy D. Wortzel [b], Areebah Naeem [b], Varun Warrier [c], Sinan Guloksuz [d,e], Ran Barzilay [a,b,f,*]

[a] Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA
[b] Lifespan Brain Institute of the Children's Hospital of Philadelphia (CHOP) and Penn Medicine, Philadelphia, USA
[c] Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridgeshire, UK
[d] Department of Psychiatry, Yale University School of Medicine, New Haven CT, USA
[e] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands
[f] Department of Child and Adolescent Psychiatry and Behavioral Science, CHOP, Philadelphia, USA
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*Correspondence concerning this article should be addressed to Ran Barzilay, Perelman School of Medicine, University of Pennsylvania, 3400 Spruce St. – 10th Floor Gates Pavilion, Philadelphia, PA 19104. E-mail: ran.barzilay@pennmedicine.upenn.edu

Abstract

Environment is key to human development, yet the complex network structure of exposures (i.e., exposome) makes it challenging to investigate. Here, we analyzed data from the Adolescent Brain and Cognitive Development (ABCD) Study – a large, diverse sample of US adolescents (N=11,235, mean age=10.9, 52% male) with phenotyping at multiple levels of environmental exposure. Applying data-driven iterative factor analyses and bifactor modeling, we reduced dimensionality from hundreds of exposures to six exposome subfactors and a general (adverse) exposome factor. These factors revealed quantitative differences among racial and ethnic groups. Exposome factors increased variance explained in mental health by 10-fold (from <4% to >38%), over and above other commonly used sociodemographic factors. The general exposome factor was associated with psychopathology (Beta=0.27) and key health-related outcomes: obesity (OR=1.4) and advanced pubertal development (OR=1.3). Findings highlight the exposome's role in adolescent health and demonstrate the critical need to study environment using the exposome framework.

Introduction

Environment (E) is a key driver of variability in human development[1], with extensive literature linking environment to general[2] and mental health[3]. Childhood environment is especially important for development, with evidence that exposures occurring during sensitive periods of development are critical for later life health outcomes in both animals[3] and humans[4]. Therefore, there is a clear need to characterize environment in a systematic and comprehensive manner early in the lifespan to advance our understanding of its role in human development.

A major challenge in studying environment's associations with health and disease is that exposures are often co-occurring and collinear[5], and it is difficult to disentangle specific effects because they are intertwined in a complex, dynamic network[6]. For example, when studying exposure to trauma, one should consider its correlation with poverty, neighborhood environment, familial factors, and much more. Thus, it is difficult to dissect specificity in relationships between single exposures (e.g., trauma) and developmental outcomes. Furthermore, exposures are not isolated and are likely to interact both amongst themselves (ExE) and with genetics (G) (GxE) to drive developmental outcomes, as proposed in various developmental models (e.g., "stress-diathesis"[7], "stress inoculation"[8], "developmental origin of health and disease"[9]).

The exposome paradigm is one framework that may advance the study of environment[10]. First coined by Wild in 2005[11], the exposome represents the totality of environmental exposures that an individual experiences from conception throughout the lifespan[12], as well as the interaction between these exposures[6]. Though early studies of exposome effects on health were focused on physical exposures (e.g., chemical carcinogens) on cancer risk[13], the concept has recently been extended to psychiatry[14], with evidence of exposome effects in both psychosis[15] and suicide research[16].

While effects of specific environmental exposures have long been studied in medicine using hypothesis-driven approaches[17], there is a need for research that investigates the exposome in its entirety. Specifically, there is a gap in large-scale studies of the exposome's role in child and adolescent development. The Adolescent Brain and Cognitive Development (ABCD) Study follows a large, diverse cohort of children (N=11,878, recruited at age 9-10) ascertained through school systems and spanning almost the entire geographic United States, including both urban and rural settings[18]. ABCD Study protocol collected data on environment at multiple levels of exposure including household, family, school, neighborhood, and state[19]. Given several hypothesis-driven studies that have examined specific ABCD exposures' effects on brain and behavior outcomes (e.g., trauma[20], neighborhood poverty[21], air pollution[22], prenatal cannabis exposure[23], screen time[24], family factors[25]), there is a need for a holistic approach that can leverage the data to generate measures that will capture the exposome comprehensively, test its relationship with mental and general health measures, and facilitate integration of exposome measures in studies of human development.

In this analysis, we used data from the 1-year follow-up ABCD Study assessment (N=11,235, see **Supplemental Table 1** for demographics), which included youth- and parent-report of children's exposures and census-level data[19]. We applied a series of factor analyses to allow data dimensionality reduction and generation of exposome factor scores. In view of the exposome paradigm that a myriad of environmental exposures drives variability in health outcomes, we aimed to (i) comprehensively and systematically characterize the exposome (i.e., the combined effect of exposures at multiple levels of analysis) of early-adolescents in the US; (ii) generate exposome scores that represent environment and can be used for downstream analyses; and (iii) test its associations with mental health and indicators of general health, over

and above commonly used proxies of socioeconomic environment (parent education and household income). For health outcomes, we focused on obesity, a key risk factor for later lifespan morbidity[26], and pubertal development, considering studies linking earlier puberty with poorer health outcomes[27]. **Figure 1** depicts the overall study design.

[INSERT **Figure 1** HERE]

Methods

Participants

The ABCD sample includes 11,878 children aged 9–10 years at baseline, recruited through school systems[28]. For the purposes of this study, 1-year follow-up data was used (N=11,235). Participants were enrolled at 21 sites, with the catchment area encompassing over 20% of the entire US population in this age group. All participants gave assent. Parents/caregivers signed informed consent. The ABCD protocol was approved by the University of California, San Diego Institutional Review Board (IRB), and was exempted from a full review by the University of Pennsylvania IRB. See **Supplemental Table 1** for full demographic data.

Measures

We included a total of 798 variables that tap participants' environmental exposures at multiple levels of analysis including family-, household-, school-, extracurricular-, neighborhood-, and state-level, as well as prenatal exposures. We included measures based on both youth- and parent-report, as well as geocoded address. We did not include genetic data as we focused on environmental exposures in this project. Additionally, we did not include imaging or neurocognitive data. Imaging procedures and the comprehensive ABCD Study neurocognitive assessment were not conducted in the ABCD Study time point used in the current exposome analysis (i.e., the 1-year follow-up assessment). **Supplemental Table 2** provides the full range of exposure measures used in the present study.

For the models testing associations of exposome scores with psychopathology (*P-factor*), we used variables tapping mental health (n=93, see **Supplemental Table 18** for the full list) comprising youth self- or caregiver-reported attitudes, experiences, and problems. For models

testing the exposome's association with obesity and pubertal development, we used BMI and pubertal development data (measure pds_y_ss_female_category_2 and pds_y_ss_male_cat_2). All measures were collected at the ABCD 1-year follow-up assessment.

Statistical Analysis

The analytic plan and hypotheses were preregistered on Open Science Framework in October 2020, before the full release of ABCD 1-year follow-up data. Analyses were conducted from January to July 2021, following ABCD data release 3.0, which was the first full release of the 1-year follow-up data and included youth-reported life events and discrimination. We used Mplus 8.4[29] for factor analyses and SPSS statistical package version 26.0 for all other statistical methods. Statistical significance was set at $P<0.05$.

Handling of missing data

Models testing associations of the exposome with psychopathology, obesity, and pubertal development used listwise deletion of missing data. All other analyses use pairwise deletion.

Dimensionality reduction of environment

Due to the large number of ABCD variables of multiple formats (continuous, ordinal, and nominal) and from multiple measures (youth-report scales, parent-report scales, census-level composites, etc.) of different lengths (scales used in the ABCD Study ranged from 2 to 59 items in length), the process of arriving at an optimal ABCD exposome model was complex. **Supplemental Figure 1** presents a visual schematic of the steps taken to reduce dimensionality of variables. We started with 798 variables, from which we selected certain ABCD-provided

summary variables according to a combination of *a priori* knowledge (e.g. similar decisions had to be made about the American Community Survey in our previous works[30]) and common sense, ultimately collapsing variable count to 348. We often chose to use summary scales to represent overarching culture and environment (e.g., Mexican American Cultural Values Scale, family conflict) and indicators of health (e.g., family psychiatric history, dietary habits). We included these in the following analysis and, using multiple exploratory factor analyses (EFAs), iteratively reduced the number of variables. We elaborate below, but the first iteration is representative of later iterations. It proceeded as follows:

1. Estimate a mixed correlation matrix where each bivariate relationship in the matrix is appropriate to the variable types. If two variables are continuous, use a Pearson correlation; if they are both dichotomous, use a tetrachoric correlation; if they are both ordinal (or one ordinal and one dichotomous), use polychoric; if one is continuous and the other dichotomous, use biserial; and if one is continuous and the other ordinal, use polyserial.

2. Determine the number of factors to extract based on subjective evaluation of the plot of descending eigenvalues (scree plot). That is, visually, subjectively determine where on the scree plot the decreasing function begins to form a linear trend (find the "elbow"). **Supplemental Figure 2** shows an example of a scree plot for determining the number of factors to extract.

3. Estimate an EFA model using least-squares extraction and oblimin rotation.

4. Examine the solution for interpretability, with particular attention to groups of variables so strongly related that they should be reduced. For example, if a factor comprised items from only one scale, with very high loadings on that factor and near-zero loadings elsewhere, that would suggest the scale could be reduced.

5. Use secondary factor analyses to reduce the groups of variables discovered in #4 above. For example, if all items from a checklist of negative life events loaded together in the solution in #4 above, submit that checklist to its own factor analysis. As in the main analysis, choose the number of factors based on subjective evaluation of the scree plot, calculate the appropriate correlation matrix (if a yes/no checklist, tetrachorics would be used), and use least-squares extraction with oblimin rotation.

6. Reduce the variables from #4 and #5 above by creating composite scores. In the present study, these composites were calculated using the following rules: a) if variables are dichotomous, take the mean to get a proportion endorsed; b) if variables are ordinal, z-transform them and take the mean; c) if variables are continuous, calculate factor scores (oblique Thurstone/regression method) from the model in #5 above.

7. Replace the variables discovered in #4 above with the variables created in #6 above. Using this updated data set, go back to #1 and repeat.

In the present study, the above steps were repeated 9 times (**Supplemental Tables 3-11**) to arrive at a set of 96 variables with minimal redundancy. Next, we estimated an EFA solution using the "clean" 96-variable dataset obtained from the iterative process described above. A unique aspect of this step was that, because we expected complex structure whereby some cross-loadings would be substantial and meaningful, we used iterated target rotation (ITR)[31,32] rather than a simple structure rotation like oblimin or promax. Whereas simple structure rotations attempt to get p-1 elements in each row as close to zero as possible (where p = number of factors), ITR allows salient cross-loadings to be estimated freely. It starts with a simple structure rotation (here, oblimin), uses the resulting pattern matrix to determine not only which item loads where but also which cross-loadings might be non-negligible, and builds a partially-specified

target matrix that incorporates cross-loading items[33]. Specifically, it uses a user-defined threshold (here, 0.20), sets all elements of the target matrix at 0 for items loading below that threshold, and sets all other (non-negligible) loadings to "unspecified" (indicating they should be estimated freely). The results of this target rotation are then used in the same way as the original simple structure rotation to specify a new target, and the process is repeated. When a new target matrix matches a previous target matrix in the iterative process, the ITR solution has converged.

With the EFA solution obtained from the above ITR process, we went on to define a quasi-confirmatory bifactor analysis from which ABCD exposome factor scores could be obtained. The bifactor model confirmatory factor analysis (CFA) was estimated in Mplus using the wlsmv estimator, accounting for clustering by family. A bifactor model uses a factor configuration whereby each variable loads not only on its specific factor (e.g., a measure of family poverty might load on a "household adversity" factor), but also on a general exposome factor comprising (with estimated loadings on) all variables. Note that this analysis reduced the included items from 96 to 65 according to significance of within-factor association. A visual presentation of the exposome bifactor solution is presented in **Figure 2**.

Some aspects of our approach are unique and require clarification. First, it is important to state why we used a CFA on the same sample as was used for the EFAs, whereas it's typical to perform EFAs on a training sample to provide a configuration that CFA can then confirm in a separate sample. If we wished to make a claim about the "true" theoretical structure of the exposome, then a cross-validation framework would be optimal, as was done, for example, in Moore et al. (2020) to make claims about the true theoretical structure of psychopathology.[34] However, we conceptualize the exposome here as a bottom-up collection of phenomena which define it (the exposome) *ad hoc*. If additional variables were added to the analysis (e.g.,

prevalence of venomous snakes in the area or affordability of local fresh vegetables), the definition of the exposome itself would change. This is in contrast to, for example, depression, whose definition does not change when indicators are added; additional indicators simply increase the precision of measurement. In this sense, the goal of the present study was simply to calculate scores for use in downstream analysis (as shown in this study with the exposome factors' association with psychopathology, obesity, and pubertal development), and confirmatory bifactor modeling allowed optimal estimation of those scores. Furthermore, it is important to clarify why a confirmatory model was used to calculate scores as opposed to the original, exploratory model. CFA was used here because, as of this study, there is no good bifactor rotation available. The most common "bifactor" rotation, the Schmid-Leiman, is not a true bifactor. It estimates a higher-order solution and transforms that to a bifactor configuration, which necessitates proportionality constraints on the solution. Another option is the Jennrich-Bentler true bifactor rotation[35], which has been shown to perform poorly in multiple studies to date[36]. It is therefore preferred to use a confirmatory bifactor model to obtain scores.

A second aspect of our approach that requires explanation is the decision to use a bifactor model at all, given the weak inter-factor correlations found in the final EFA (see **Results**). Bifactor modeling accounts for inter-factor correlations by modeling the overall factor as its own phenomenon, unlike, for example, orthogonal EFA rotations (like varimax), which force orthogonality onto solutions without accounting for the true obliqueness of the phenomena. Usually, one of the indications that a bifactor model might be useful is moderate-to-strong inter-factors correlations, which suggest the existence of an overall, general factor underlying all item responses[37]. Here, inter-factor correlations were weak, suggesting that there may not be a hierarchical structure to environmental exposures (neither second-order nor bifactor). However,

in addition to common sense suggesting that adverse environments at the distal level beget adverse environments at the proximal level, there is increasing evidence that bifactor general factors can contain critically important information even when inter-factor correlations are weak[38]. This is possible because, while the subfactors of a model might correlate only weakly, individual items within each subfactor may still load strongly on the general factor. The above-cited example demonstrates not only that such a phenomenon exists, but that the general factor scores generated from the seemingly ill-advised models have substantial validity.

Association of exposome scores with demographic characteristics

For comparisons of exposome scores within each demographic variable (males vs. females, high vs. low parent education and household income, and comparisons across race and ethnicity), we used t-tests (Bonferroni corrected for seven comparisons), with Cohen's d to estimate effect size.

Generation of P-factor

The exposome analyses required some special modeling due to the mixture of variable formats (continuous, ordinal, etc.) and expected complex structure. By contrast, because all psychopathology variables (n=93) in this study were items (youth self- or caregiver-reported attitudes, experiences, and problems; see **Supplemental Table 18** for the full variable list), they could be analyzed entirely within an item-factor analysis framework[39] whereby all correlations are polychoric rather than being a mix of types. This analysis (using oblimin rotation) revealed that the psychopathology items clustered exactly by instrument (i.e., questionnaire/scale), with only two cross-loadings >0.30; see **Supplemental Table 19**). The "clean" solution supports our

use of a simple structure rotation. All items thusly grouped by instrument form a 6-factor solution. Specifically, *Factor 1* comprises variables most related to symptoms of psychosis and associated prodrome. *Factor 2* comprises variables most related to suicidal ideation or attempt (suicidality). *Factor 3* comprises variables most related to externalizing symptoms. *Factor 4* comprises variables most related to manic symptoms. *Factor 5* comprises variables most related to self-reported (mostly internalizing) symptoms. *Factor 6* comprises variables most related to positive affect.

The results of the configuration above were taken as the basis of the confirmatory model used to calculate the *P-factor* score using a bifactor model CFA estimated in Mplus using the wlsmv estimator, accounting for clustering by family. **Supplemental Table 20** details results from confirmatory bifactor model analysis, displaying specific factor loadings as well as loadings to a general psychopathology factor. Overall, fit of the model was acceptable (CFI=0.93; RMSEA=0.023; SRMR=0.085), and these results are presented visually in **Supplemental Figure 3**. This general *P-factor* score was used for subsequent correlational analyses with the exposome factor scores.

Associations of exposome scores with the mental health

We tested the association of exposome scores (the general *Exp-factor* and the six orthogonal subfactors) with the *P-factor* (dependent variable in the main analysis) and with total CBCL t-score (in sensitivity analysis) using a linear regression with the seven exposome factors as independent variables and age, sex, parent education, household income, race (White, Black, Asian, Other), and Hispanic ethnicity as covariates. The model was also run without the

exposome scores to estimate the change of adjusted R^2 upon addition of exposome scores to the model.

Association of exposome scores with obesity and pubertal development

We tested the association of exposome scores (the general *Exp-factor* and the six orthogonal subfactors) with obesity or pubertal development (two separate models) using a binary logistic regression model with obesity (binary variable, BMI percentile>=95); or with late/post-pubertal status (binary variable contrasted against pre-/early-/mid-pubertal status) as the dependent variables, and the seven exposome factors as independent variables, co-varying for age, sex, parental education, household income, race (White, Black, Other), and Hispanic ethnicity. The pubertal development model also co-varied for BMI.

Results

Dimensionality reduction of the exposome in ABCD Study

We identified a comprehensive set of environmental exposures in the ABCD Study (798 variables, **Supplemental Table 2**). In line with our goal to comprehensively assess environment and the exposome paradigm that multiple exposures combine to explain variance in health outcomes, we applied a permissive definition of environment. For example, since parental factors play a major role in childhood development, we included parental psychopathology in our analyses, even though we acknowledge that genetic contributions of parental psychopathology also exist in the child. Furthermore, because we wanted to investigate the utility of applying an exposome framework, we excluded two pivotal measures commonly used to estimate environment, including in previous ABCD Study research: household income[40,41] and parental education[42]. This choice allowed us (1) to test the "added value" of the exposome scores to explain variance in health outcomes over and above commonly used proxies of environment known to associate with developmental outcomes[43], including in ABCD Study[41]; and (2) to validate the exposome scores using "classic" indicators of socioeconomic environment.

From the 798 identified environmental variables, we decided on features for which to use ABCD summary measures (e.g., family conflict; see detailed description of variable choice in **Methods**), resulting in 348 variables for analysis. Then, we applied a set of exploratory factor analyses (EFAs) to identify correlation-based clustering among variables and allow further reduction of variable number. **Supplemental Figure 1** provides a schematic presentation of this dimensionality reduction process, which is described in full in **Methods**. Briefly, we started by including all 348 variables in analysis and, using nine EFAs, iteratively reduced these to 96 with minimal redundancy. Each of the EFAs described above included items from subdomains of

environmental exposures, including parental mental health and drug use (**Supplemental Table 3**), maternal substance use during pregnancy (**Supplemental Table 4**), neighborhood-level characteristics (**Supplemental Table 5**), household-level poverty and religiosity (**Supplemental Table 6**), school-level characteristics (**Supplemental Table 7**), pregnancy complications (**Supplemental Table 8**), birth complications (**Supplemental Table 9**), parent-report of childhood traumatic events (**Supplemental Table 10**), and youth-report of life events (**Supplemental Table 11**).

Table 1 shows the results of the final EFA of the minimally redundant 96 environmental variables, using iterated target rotation (ITR) designed to detect complex structure (cross-loadings), which revealed six factors. *Factor 1* comprises variables most related to *household adversity*, based primarily on parent-report, with the strongest indicators being the mother's use of tobacco or marijuana during pregnancy, parental alcohol-related problems affecting ability to hold a job or stay out of jail, and frequent adult conflict in the house. *Factor 2* comprises variables most related to *neighborhood environment*, based primarily on geocoded address, with the strongest indicators being census-derived measures of neighborhood poverty and population density. *Factor 3* comprises variables most related to youth-reported *day-to-day experiences*, both positive (e.g., feeling "involved at" and enjoying school, acceptance by caregivers) and negative (e.g., experiences of discrimination, family conflict). *Factor 4* comprises variables most related to *state environment*, with the strongest indicators being negative attitudes toward persons with non-hetero sexual orientation, traditional views about the roles of women, and less permissive marijuana laws. Note that a "ruralness" aspect of *Factor 4* is evident in the low neighborhood wealth and property values (seventh indicator from top). *Factor 5* comprises variables most related to *family values*, with the strongest indicators being the strictness of rules

related to alcohol, tobacco, and marijuana, as well as various indicators that tap importance of religion and family cohesiveness. *Factor 6* includes variables most related to *pregnancy and birth complications*, with the strongest indicator being premature birth. Of note, prenatal exposure to substances did not load on *Factor 6*, but rather on *Factor 1* which taps household adversity. This configuration was used because it indicates that maternal substance use is more revealing of household adversity than of pregnancy or birth complications. Inclusion of maternal substance use in *Factor 6* would, paradoxically, increase the ambiguity of that factor.

[INSERT **Table 1** HERE]

We then conducted a quasi-confirmatory factor analysis (CFA) model that included 65 items, selected from the 96 variables based on their loadings in the EFA ("quasi-" because there is no cross-validation being performed here; the "confirmatory" model is actually being used to estimate a model for score creation rather than truly confirm a theoretical or empirically-derived model)[44]. Specifically, items with absolute value less than 0.30 in the ITR-rotated EFA (**Table 1**) were removed for the final CFA analysis used for creation of exposome scores. These selected 65 items inform the resultant general exposome factor and were derived from multiple scales of the ABCD Study, from both parent- and youth-report and from census-derived measures.

Generation of exposome scores

To estimate a general exposome factor *(Exp-factor)* score and orthogonal exposome subfactor scores that allow delineation of discrete environmental effects on development, we applied a bifactor modeling approach[37]. **Figure 2** shows the results of the quasi-confirmatory

bifactor analysis with the loadings of the strongest items and their direction (see full list of item loadings in **Supplemental Table 12)**. Fit of the model is acceptable, with a root mean-square error of approximation (RSMEA) of 0.033 and standardized root mean-square residual (SRMR) of 0.060; confidence intervals around the RMSEA were imperceptibly narrow at this sample size. Note that the comparative fit index (CFI) of 0.85 was below the acceptable range, conflicting with other fit indices, which is a known phenomenon in large models[45] and likely does not indicate poor fit[46]. Here, it was possible to achieve a CFI > 0.90 *post hoc* by allowing some residuals to correlate, but we opted to leave the model "pure" rather than use modification indices[47] merely to increase one fit index. Thus, the *Exp-factor* captures the broad, multidimensional environmental phenotyping of the ABCD assessment. Notably, extreme household poverty, parental legal trouble, unplanned pregnancy, physical conflict among adults in the household, neighborhood poverty, and experiences of discrimination were among the strongest loading items of the *Exp-factor*. Also of note, in the EFA model (**Table 1**), experiences of discrimination loaded strongly on the *day-to-day experiences factor*, but in the bifactor model (**Figure 2**; **Supplemental Table 12**), variance explained in the discrimination items "shifted" from *day-to-day experiences* to the *Exp-factor*. Thus, in the final model, most discrimination is accounted for by the *Exp-factor* score. The *day-to-day experiences* subfactor is left without discrimination and is heavily influenced by attitudes toward school, a center-point of life in this age range.

[INSERT **Figure 2** HERE]

The exposome across sociodemographic groups

Next, we tested the associations of the *Exp-factor* and the six exposome subfactor scores with key sample demographics. **Figure 3** shows comparisons of the exposome scores across sex, household income, parental education, race, and ethnicity. Sex differences did not emerge in the *Exp-factor* or in five of the six subfactors; the only difference was that males had greater *day-to-day experiences* scores (Cohen' *d*=0.30, P<.001), which is driven by the fact that males report disliking school more often than females do. Comparison of high to low parent education and household income revealed expected differences, whereby both were associated with greater *Exp-factor* score with very large effect sizes (for income, *d*=1.40; for parent education, *d*=1.16, P's<0.001), and greater *neighborhood environment* (poverty) scores with medium effect size (for income, *d*=0.63; for parent education, *d*=0.41, P's<0.001). Comparison of high/low parent education and income of other exposome factors including *household adversity*, *family values*, and *state environment* revealed differences in the small effect size range (*d*'s ranging from 0.10-0.22, all P's<0.001). Notably, comparing high/low income and parent education revealed either very small (d's<0.09), or non-significant differences in the *day-to-day experiences* subfactor and the *pregnancy/birth complications* subfactor (**Figure 3**).

Comparison of the *Exp-factor* score across races and ethnicities revealed striking differences. Black participants (n=2,269) had greater *Exp-factor* scores than non-Black participants (n=8,966) in the very large effect size range (*d*=1.28, P<0.001); Hispanic participants (n=2,226) also showed greater *Exp-factor* scores than non-Hispanic participants (n=8,872), but with a smaller effect size (*d*=0.29, P<0.001). Notably, Asian participants (n=723) had lower *Exp-factor* scores than non-Asian participants (n=10,512), with a medium to large effect size (*d*=0.66, P<0.001). Comparisons of exposome subfactors across races and ethnicities showed that the only difference with a large effect size was observed in Hispanic participants,

who had a greater *neighborhood environment* subfactor score (representing greater population density and, to a lesser extent, poverty) (*d*=0.92, P<0.001). Similarly, Black and Asian participants showed greater *neighborhood environment* subfactor scores, but with smaller effect sizes (for Black, *d*=0.41; for Asian, *d*=0.28, P's<0.001). Comparison of the *state environment* subfactor revealed differences among races and ethnicity at the small to moderate effect size range (*d*'s ranging from 0.25-0.43). Differences in *family values* subfactor scores were observed among Black and Hispanic, but not Asian participants, who were the only group that showed differences in the *birth/pregnancy complications* subfactor, with lower scores. Notably, no differences were observed in *day-to-day experiences* (largely determined by attitudes toward school) when comparing across races and ethnicities. (**Figure 3**).

[INSERT **Figure 3** HERE]

Association of exposome scores with mental health

We next sought to use exposome factor scores to explain variance in participant mental health. First, we generated a single general factor score that represents the overall liability to psychopathology (*P-factor*)[48,49], which was consistently shown to accurately represent psychopathology in youth samples[50]. Then, we used the exposome scores as independent variables to test their contribution to explaining variance in *P-factor* (dependent variable). We found that while age, sex, race, ethnicity, household income and parent education explained <4% of the variance in *P-factor* score, the addition of the exposome factors increased the variance explained ~10 fold to 38.2% (**Table 2**). Among the exposome factors, *day-to-day experiences* showed the greatest association with *P-factor* score (Standardized Beta=0.516, P<0.001),

followed by the *Exp-factor* (Standardized Beta=0.276, P<0.001). Other exposome subfactors were also significantly associated with *P-factor* score, but with relatively modest effect sizes (all betas<0.09, all P's<0.025). The single subfactor not associated with *P-factor* score was *pregnancy/birth complications* (p=0.075).

[INSERT **Table 2** HERE]

Association of exposome scores with youth obesity and pubertal development

Lastly, we tested whether exposome scores are associated with general adolescent-health indicators that are important for health later in the lifespan: obesity[26] and pubertal development[27], which are both influenced by the environment[51,52]. Overall, 1,871 (16.7%) in the cohort were obese based on U.S. Centers for Disease Control (CDC) definitions (body mass index [BMI]>95th percentile)[53]. 727 youths (6.5% of sample, n=104 males [1.7% of males], n=623 females [11.5% of females]) were late/post-pubertal (4/5 on a 5-point Likert scale). The *Exp-factor* was significantly associated with obesity and with late/post-pubertal status (odds ratio [OR]=1.41, 95%CI=1.31-1.52; OR=1.30 95%CI=1.16-1.47, respectively, P's<0.001; **Figure 4** and **Supplemental Tables 13-14,** models co-varied for demographics, household income, and parental education, and BMI in the puberty model). No exposome subfactors were associated with obesity. The *day-to-day experiences* subfactor was the only one significantly associated with late/post-pubertal status (OR=1.31, 95%CI=1.19-1.43, P<0.001).

[INSERT **Figure 4** HERE]

Sensitivity Analyses

Associations of exposome factors with parent-reported child psychopathology (using the total child behavior checklist [CBCL] t-score) revealed similar findings to main analyses, whereby the addition of the exposome factors increased the explained variance by ~7 fold to 17.8%, compared to 2.5% in the model relying on demographics, household income, and parent education (**Supplemental Table 15**). Using continuous measures of weight (BMI percentiles) and puberty (1-5 Likert scale) rather than binary outcomes, results were similar in direction and statistical significance to the main analyses **(Supplemental Tables 16-17)**.

Discussion

We provide a comprehensive investigation of the exposome in early adolescence in the US. We show that a data-driven approach allows integration of multiple exposures, resulting in dimensional factors representing different facets of the exposome, and that these factors explain variance in early adolescent psychopathology, obesity, and pubertal development. Our findings allow for the appreciation of quantitative differences among American children's environments across sociodemographic groups, which are likely to impact their trajectories of mental and physical development throughout the lifespan[54,55]. Notably, a major finding is that, within orthogonal exposome subfactors, significant items loaded from different measurement tools and levels of analysis (parent- and youth-report, individual-level exposures, and census-derived variables). This suggests that specific exposures within exposome factors likely represent a shared latent factor, highlighting the need to use a theoretical exposome framework when studying environmental effects on health[10]. Furthermore, bifactor modeling of the exposome revealed a general exposome adversity factor that integrates multiple exposures in addition to orthogonal exposome subfactors, which together provide a roadmap for dissection of specific

environmental effects on developmental outcomes while accounting for the exposome's complexity.

Our study is important for various reasons. *First*, it demonstrates how inevitably collinear exposures can be modeled when they are captured at multiple levels. For example, the *household adversity* subfactor had strong loadings on youth-report of parental trouble with the law, parental self-reported psychopathology, developmental history (capturing prenatal exposure to cannabis), and parent-report of poverty and whether their pregnancy was planned. Therefore, when trying to dissect developmental effects of specific exposures based on a priori knowledge and hypotheses in the ABCD Study, one should account for the collinearity that is likely to confound any relationship a specific exposure may have with an index outcome of choice. *Second*, our results suggest that data-driven approaches to characterize the exposome may be important to reveal latent factors that cannot be identified with a priori knowledge. A key example of this phenomenon in the analysis is the prenatal exposure items, from which items split between the *household adversity* subfactor (prenatal exposure to substances, planned pregnancy) and the *pregnancy/birth complications* subfactor. Notably, growing efforts try to link pre-/post-natal exposures in the ABCD Study with developmental outcomes (prenatal cannabis exposure[23], breastfeeding[56] and other prenatal adversities[57]). Hence it will become increasingly important to rigorously account for exposome complexity to allow generalizability and replicability of findings and identify causal mechanisms that are not confounded by collinear exposures. *Third*, in the context of understanding variance in psychopathology, our findings provide compelling evidence for the critical need to include environmental exposures when modeling psychopathology outcomes (~10-fold increase in R^2 explaining psychopathology [*P-factor*] upon addition of exposome factors), over and above the commonly used estimators of socioeconomic

environment (parent education and household income). *Fourth*, our finding on exposome contribution to variance in obesity and pubertal development provides a proof-of-concept for the utility of studying exposome effects on health trajectories in ABCD participants as they mature.

Previous research in other youth cohorts supports the notion that different exposures (e.g., trauma and neighborhood SES) and different mechanisms of environment (threat vs. deprivation) are differentially associated with brain and behavior outcomes[58,59], highlighting the need to address environmental complexity. For example, growing literature supports the notion that different exposures specifically shape distinct brain structures and networks[60]. The deep phenotyping of multiple environmental facets in the ABCD Study creates unprecedented opportunities to specifically link environmental effects to brain and behavior development. Recent ABCD studies have provided proof-of-concept for brain-behavior-environment analyses that map neural parameters to multiple exposures[61,62], and for the potential to use a subset of environmental risk factors to explain variance in mental health outcomes[63]. In addition, several studies have reported associations of specific exposures with cognition and neuroimaging parameters in ABCD data (e.g., household income[41], neighborhood disadvantage[64], lead exposure[40]). The studies mentioned above all used baseline ABCD data, which does not include key environmental exposures. The current study expands on previous works as we used 1-year follow-up data, which included youth-reported exposures (negative adverse life events and experiences of discrimination) not captured at baseline. Notably, these items had high loadings on the *Exp-factor* and represent a total of 5 exposures among the top-loading 13. The fact that the *Exp-factor* explains substantial variance in both mental and general health indicators emphasizes the need to incorporate youth-report when studying the exposome.

We suggest that this study be a roadmap when modeling environment in future ABCD Study investigations of developmental trajectories using multimodal (e.g., imaging, cognitive) longitudinal data. Notably, the current study does not study the exposome's associations with cognitive and imaging measures, which should be investigated in future works. Additionally, exposome scores can be used to explore interactions within the exposome (ExE), which have been shown to exist in association with baseline ABCD cognitive and imaging outcomes[40]. Similarly, exposome scores can be used as covariates to adjust for nuisance environmental variance in studies with smaller samples or when trying to dissect the link between a specific exposure and an outcome. Moreover, we suggest that integration of genetic data with the exposome scores can facilitate better modeling when studying GxE mechanisms in ABCD participants, allowing researchers to reliably measure environment (with all its complexities) as dimensional environmental burden in conjunction with polygenic risk scores as dimensional genetic burden[65,66]. Lastly, our findings reveal large quantitative differences in latent environmental factors that illuminate dipartites among demographic groups in America, which likely relate to disparities in later lifespan health outcomes[67]. We suggest that the exposome scores can be used to identify high-risk groups that are more difficult to identify using a priori knowledge. Studies of such subpopulations are critical in the effort to tease apart mechanisms of resilience[68], which are themselves influenced by multiple dimensions of environment (i.e., intrapersonal, family, neighborhood)[69], and therefore require investigation in a wide environmental context.

A few methodological considerations we took are worth discussion. First, when determining environmental variables to include in analysis, we generally tried to take an inclusive approach informed by literature on environmental effects on development[2,70,71]. We

included some variables that have substantial genetic components (e.g., parent psychopathology) and others that are confounded by psychopathology (e.g., school enjoyment). We chose not to include substance use variables, which were considered as "psychopathology indicators" rather than environmental exposures. Second, we chose to use a bifactor model to fit the exposome data. This was largely in anticipation of a general exposome factor whereby all exposures would correlate. This model also produces orthogonal scores useful in downstream analyses to interpret specific effects. These decisions are detailed in full in **Methods**.

Limitations

Our findings should be viewed considering several limitations. First, we acknowledge that although we attempted to include all possible environmental factors in the ABCD data, we nevertheless had to follow a reasoned decision-making process to determine what exactly to include in our analyses. We also decided, in instances, to use ABCD Study composite scores as opposed to raw scores. These decisions could have influenced results. Nevertheless, the current analysis provides, to our knowledge, the most comprehensive evaluation of environment in the ABCD Study to date and relies on the most updated data release which includes youth-report of key adversities that were not included in previous studies. Second, we used cross-sectional data to test associations of the exposome factors with psychopathology, obesity, and pubertal development. Future longitudinal studies are warranted to identify causal mechanisms. Similarly, substantial parts of both the *day-to-day experiences* subfactor and *P-factor* relied on youth-report, potentially inflating the strong (>0.5) association between their scores and further muddling causal inference. Nevertheless, exposome scores explained substantial variance in mental health when using parent-report measures of youth psychopathology in sensitivity analysis. Third, there are inherent limitations to collection of environmental data, such as the

retrospective report of events and recall bias. Fourth, our study does not address the complexity of genetic contribution to environmental exposures (i.e., gene-environment correlations). This line of research is critical to address specificity of exposome effects on development and merits thorough future investigation outside the scope of the current work. Finally, we did not take a "best practice" approach to the factor analyses (i.e., split the sample, estimate an EFA model in one portion, and test the EFA model in a CFA in the other portion). However, we did not intend to test a theoretical structural model, not even the one "found" by the EFA. Instead, the purpose was to derive scores from the model that most reasonably fit the entire ABCD data set. Cross-validation of the scores will occur as they are used in downstream analyses, especially of longitudinal data.

To conclude, we leveraged a large, diverse dataset of US adolescents with deep phenotyping of environmental exposures to produce a roadmap for studying the exposome in US children. We propose that the exposome paradigm allows research to move beyond "looking under the lamp because that's where the light is" to a holistic dimensional investigation of environmental burden on development. We hope that future studies will build on the exposome framework in the ABCD Study to better understand developmental trajectories of US youths through its integration in multi-omic research of brain, behavior, and health.

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Author Contribution

TMM and RB conceptualized and designed the study, conducted the analyses, interpreted the data and drafted the first version of the manuscript. EV, STA, GED, IS, JW and AN substantially contributed to study design, organization and analysis of data and visualization of findings, and have all substantially contributed to revision of the first draft of the manuscript. VW and SG substantially contributed to study design and conceptualization, interpretation of findings, and have provided substantial input to revision the manuscript from its first draft till its final version. All authors have approved the submitted version and have agreed to be accountable to the submitted study.

Competing interest statement

Dr Barzilay serves on the scientific board and reports stock ownership in 'Taliaz Health', with no conflict of interest relevant to this work. All other authors have no conflicts of interest do declare.

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The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer

ABCD consortium investigators designed and implemented the study and/or provided data but did not participate in analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the National Institutes of Health or ABCD consortium investigators.

Additional Information

Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development Study (https://abcdstudy.org), held in the National Institute of Mental Health Data Archive. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. Data preprocessing and analysis are detailed at https://github.com/barzilab1/abcd_exposome.

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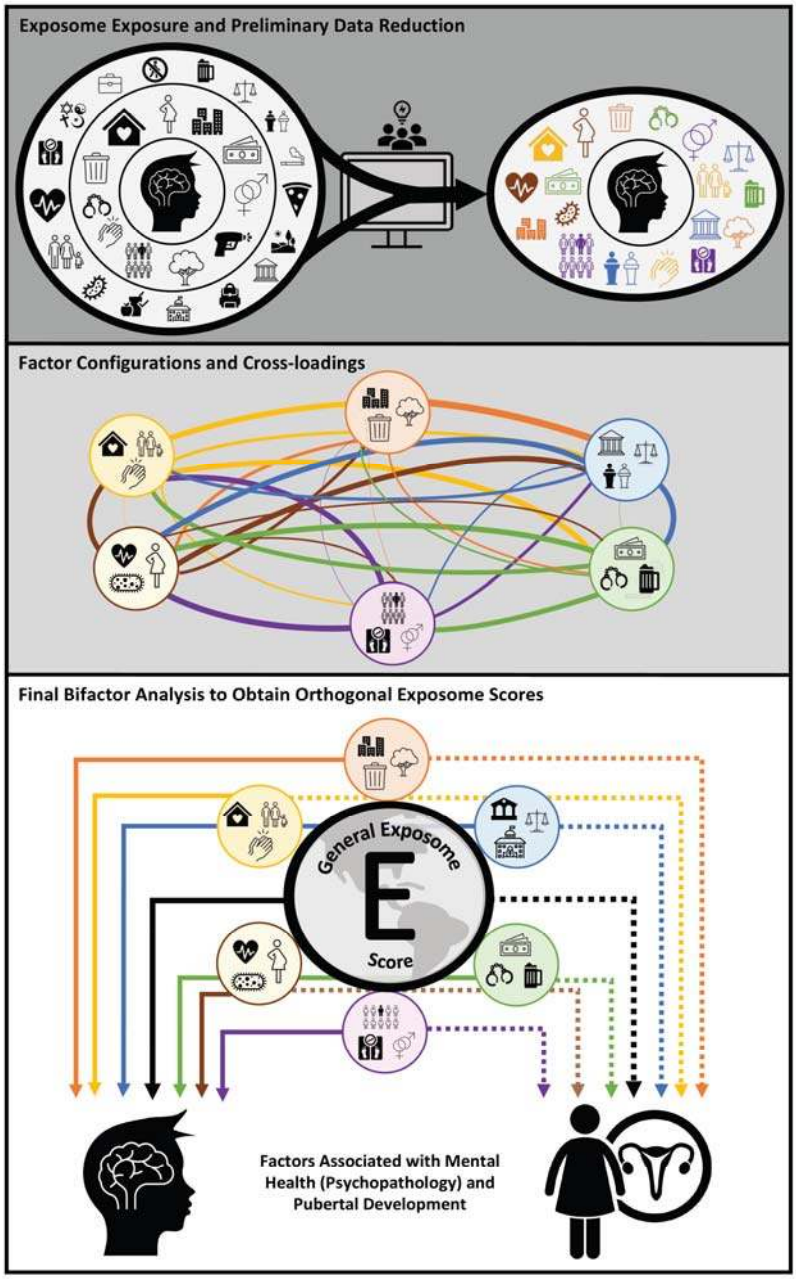
Tables and Figures

Figure 1. Visual presentation of study design.



First, 798 environmental variables from the ABCD Study were chosen for representing the multiple dimensions of the exposome. These variables were reduced to 348 variables based on choices to use ABCD Study's summary measures, and then further reduced using an iterative process of exploratory factor analyses that identified correlated factors allowing reduction to 96 variables from multiple dimensions of environment including family, household, school, extracurricular, neighborhood and state-level and prenatal and history of antenatal exposures. (top panel). Thereafter, these 96 combined items underwent an exploratory factor analysis that culminated in a final model, which finalized factor configurations and cross-loadings (middle panel), revealing 6 factors relating to the exposome (household adversity factor, neighborhood environment factor, day-to-day experiences factor, state conservatism-ruralness factor, family values factor, and pregnancy/birth complications factor). Subsequently, these factors were subjected to confirmatory bifactor analysis, which allowed the generation of a general exposome factor informed by all items, in addition to six orthogonal exposome subfactors (bottom panel). Finally, we investigated how these exposome factors are associated with mental health, body mass index, and pubertal (pre-)development.

Table 1. Exploratory factor analysis of the optimized collection of exposome items using iterated target rotation

Item	House-hold	Neighbor-hood	Day-to-day	State	Family-values	Pregnancy/ Birth complications
Prenatal exposure to tobacco or marijuana	**0.72**					
Parental lifestyle issues (e.g., trouble with holding job, police, alcohol use)	**0.69**					
Physical conflict among adults at the home	**0.64**					
Prenatal exposure to hard drugs (e.g., cocaine, heroin)	**0.56**					
Severe maternal mental health issues (e.g., breakdowns, delusions, hospitalizations)	**0.46**					
Planned pregnancy	**-0.45**	-0.23				
Severe family poverty (e.g., inability to afford necessities)	**0.45**	0.31				
Parent-reported sexual abuse	**0.44**					
Caregiver psychopathology (e.g., mood, personality, attention disorders)*	**0.41**					
Parental separation	**0.40**					
Enforced family rules for smoking cigarettes	**-0.40**					
Family legal trouble (e.g., arrests, jailtime)	**0.38**		-0.30			
Inability to afford necessary medical/dental visit	**0.38**					
Prenatal exposure to alcohol	**0.36**	-0.21			-0.20	
Parent-reported childhood trauma (e.g., accident, disaster, extreme violence)	**0.35**					
Sudden death of a loved one	**0.34**					
Severe paternal mental health issues (e.g., breakdowns, delusions, hospitalizations)	**0.33**					
Prenatal exposure to caffeine	-0.30					
Ease of access to marijuana	0.30					
Mean parental age at birth	-0.26					
Parent-reported family conflict	0.20					
Blood pressure complications at birth (e.g., Rh incompatibility, necessary blood transfusion)	0.17					
Traumatic brain injury	0.16					
Significant family lifestyle change (e.g., move, birth of new baby)	0.15					
Severe fever during first year of life	0.14					

Bed wetting	0.14				
Census-derived neighborhood poverty (e.g., unemployment rate, families/individuals below poverty level)		**0.68**			
Census-derived neighborhood population density		**0.68**			
Parental ability to speak English	0.29	**-0.66**			
Census-derived neighborhood immigration and crowding		**0.60**			
Census-derived neighborhood lead exposure risk		**0.51**			-0.24
Census-derived neighborhood walkability index		**0.51**			
Parent-reported neighborhood safety		**-0.47**			
Census-derived neighborhood air pollution (NO2,PM25)		**0.46**			
Crime reports-dervied crime prevalence (e.g., drug possession or sale, violent crime)		0.29			
Blood oxygen complications during pregnancy (e.g., severe anemia)		0.26			
Parent-reported importance of independence and self-reliance		0.25			
Parent-reported interest in ethnic background and culture		0.22			
Census-derived neighborhood proximity to major roads		-0.21			
Participation in extracurricular activities (e.g., sports, crafts, hobbies)		-0.21			
Parent-reported connection to ethnic background and culture		0.19			
Nutrition		0.16			
Weeks post-conception at discovery of pregnancy		0.10			
Youth-reported positive school involvement			**0.59**		
Youth-reported acceptance and love by primary caregiver			**0.57**		
Youth-reported school enjoyment			**0.57**		
Youth-reported racial/ethnic discrimination (past year)			**-0.57**		
Youth-reported school grades and achievement			**0.55**		
Youth-reported parental monitoring and communication			**0.54**		
Youth-reported unfair treatment on racial/ethnic grounds (lifetime)			**-0.50**		
Youth-reported positive feedback at school			**0.49**		
Youth-reported acceptance and love by secondary caregiver			**0.49**		
Youth-reported family conflict			**-0.49**		

Youth-reported lesbian, gay, bisexual discrimination (past year)			**-0.46**		
Youth-reported discrimination based on weight (past year)			**-0.45**		
Youth-reported discrimination based on being foreign (past year)		0.29	**-0.38**		
Youth-reported family discordance (e.g., loss of job, mental health issues, conflict/violence)			**-0.34**		
Youth-reported neighborhood safety		-0.25	**0.33**		
Youth-reported exposure to serious injury, illness, death (self or other)			**-0.31**		
Youth-reported exposure to mature entertainment (e.g., M-rated video games, R-rated movies)			-0.26		
Youth-reported hours of screen time per day			-0.23		
Youth-reported ratio of good to bad life events (self-rated)			0.19		
State-level indicators bias against sexual orientation		-0.31		**0.89**	
State-level indicators of sexism				**0.80**	
State-level marijuana laws				**0.77**	
State-level indicators of bias against immigrants		-0.35		**0.75**	
State-level indicators of racism				**0.70**	
State-level legality of medical marijuana				**0.67**	
Census-derived neighborhood wealth (e.g., median mortgage, rent, income)	-0.26			**-0.45**	
Parental bi- or multi-lingualism				-0.27	
Months breastfed				-0.21	
Ease of access to hard drugs				-0.17	
Family rules for using marijuana					**0.80**
Family rules for drinking alcohol					**0.76**
Family rules for smoking cigarettes					**0.74**
Parent-reported importance of religion		0.28		0.27	**0.49**
Parent-reported importance of coherence to the family unit		0.35			**0.46**
Parent-reported importance of family support		0.27			**0.45**
Parent-reported importance of obligation to family		0.31			**0.41**
Family religiosity (e.g., attendance to religious services)				0.23	**0.36**
Ease of access to alcohol or tobacco					-0.26
Enforced family rules for drinking alcohol					0.20

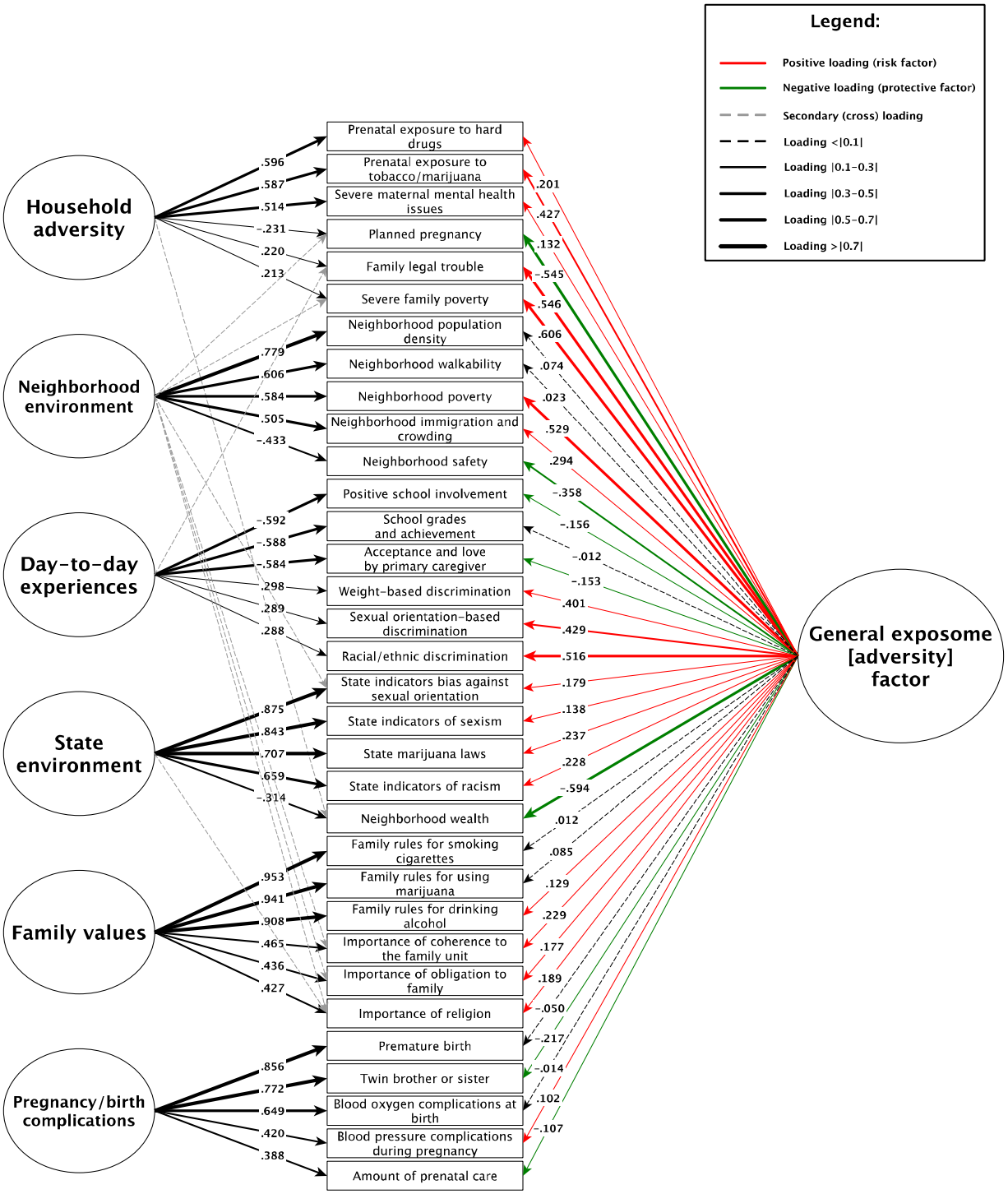
Youth-reported ostracization from American society (lifetime)			0.18			
Premature birth						**0.82**
Twin brother or sister						**0.78**
Blood oxygen complications at birth (e.g., jaundice, supplemental oxygen)						**0.60**
Time after birth in an incubator						**0.52**
Birth by caesarian section						**0.50**
Placental complications during pregnancy (e.g., previa, abruptio, persistent proteinuria)						**0.46**
Blood pressure complications during pregnancy (e.g., pregnancy-related high blood pressure, diabetes)						**0.44**
Amount of prenatal care						**0.43**
Circulation complications at birth (e.g., blue, slow heartbeat at birth)						**0.31**
Prenatal exposure to prescription medications						0.27
Developmental delay (motor/verbal)						0.24
Prenatal exposure to prenatal vitamins						0.21
Severe illness/infection during first year of life						0.13

	Inter-Factor Correlations					
	F1	F2	F3	F4	F5	F6
	1	0.16	-0.32	0.15	-0.01	0.01
	0.16	1	-0.2	0.16	0.09	-0.15
	-0.32	-0.2	1	-0.15	-0.06	-0.01
	0.15	0.16	-0.15	1	0.17	0.03
	-0.01	0.09	-0.06	0.17	1	0.02
	0.01	-0.15	-0.01	0.03	0.02	1

Results of exploratory factor analysis of the final set of exposome items, using iterated target rotation designed to detect complex structure (cross-loadings). *Factor 1* comprises variables most related to household adversity, with the strongest indicators being prenatal exposure to tobacco and/or marijuana, alcohol-related problems affecting the ability to hold a job or stay out of jail, and frequent adult arguments or "fights" in the house. *Factor 2* comprises variables most related to neighborhood environment, with the strongest indicators being objective measures of neighborhood poverty and wealth disparity, neighborhood density, and parent-reported English-speaking ability. *Factor 3* includes variables most related to day-to-day experiences, with the strongest indicators being youth-reported feeling "involved" at school, youth-reported acceptance by primary caregiver, and youth-reported enjoyment of school. *Factor 4* is composed of variables most related to state-level environment, with the strongest indicators being negative attitudes toward persons with non-hetero sexual orientation, traditional views about the roles of

women, and less permissive marijuana laws. Note that a "ruralness" aspect of *Factor 4* is evident in the low neighborhood wealth and property values (seventh strongest indicator). *Factor 5* comprises variables most related to family values, with the strongest indicators being the strictness of rules related to, 1) alcohol, 2) tobacco, and 3) marijuana. *Factor 6* includes variables most related to pregnancy and birth complications, with the strongest indicators being premature birth, a twin birth (zygosity not specified), and the child's needing supplemental oxygen after birth. Inter-factor correlations are shown at the bottom of the table.

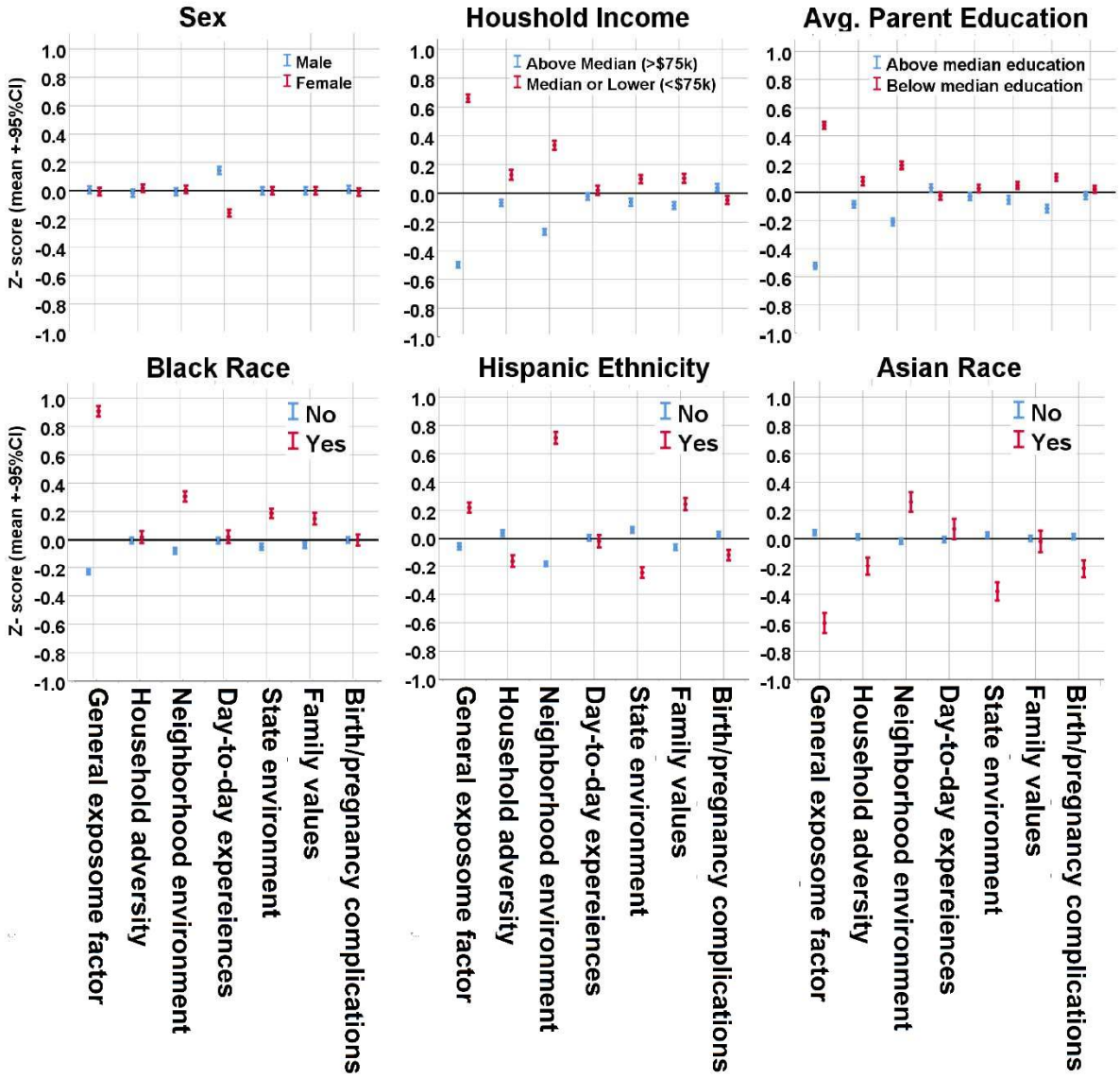
Figure 2. Exposome bifactor model



Bifactor model of confirmatory factor analysis. Only the top 3 items loading within-factor and on the *Exp-factor* are included; that is, a specific factor's indicators were included in the diagram if they were among the top three strongest-loading items on that specific factor *or* on the general factor (so maximum possible = 6 indicators per factor in the diagram). Arrow thickness relates to

the strength of the loading (higher the loading, thicker the arrow). Arrow color relates to the sign of the loading – a red arrow corresponds to positive loading (associated with a higher *Exp-factor* score; risk factor) and a green arrow corresponds to negative loading (associated with a lower *Exp-factor* score; protective factor). Subfactors are presented from top to bottom in order from F1 to F6. See **Supplemental Table 12** for the full list of items and their loadings, and for the breakdown of variables that make up each factor in the bifactor model.

Figure 3. Exposome scores across demographic comparisons



Exposome scores for the six orthogonal subfactors and one general factor are compared across demographic groups. Displayed are differences between male and female participants, high and low household income, and high and low parent education **(top panel)**, Black race, Hispanic ethnicity, and Asian race **(bottom panel)**. Demographic differences serve as an initial validation for use of generated exposome factor scores.

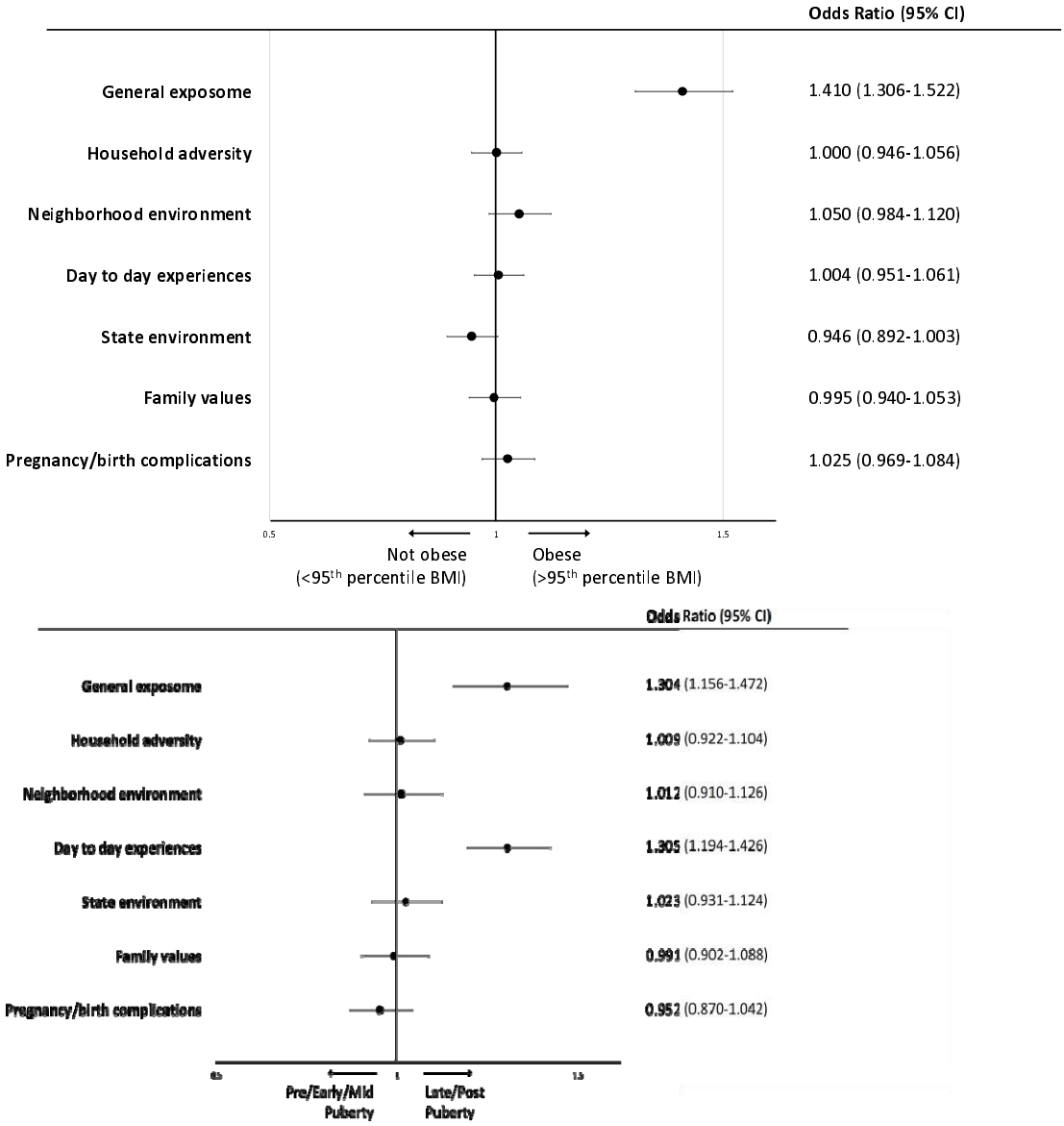
Table 2. Association of exposome factor scores to psychopathology *P-factor* score

	Model 1 (Demographics)			Model 2 (Demographics + Exposome)		
	Beta	**SE**	**P**	**Beta**	**SE**	**P**
Age (months)	-0.009	0.010	0.363	0.007	0.008	0.383
Female sex	-0.098	0.009	<0.001	-0.017	0.008	0.031
White race	0.020	0.014	0.143	-0.012	0.011	0.277
Black race	0.075	0.013	<0.001	-0.014	0.011	0.224
Asian race	-0.012	0.008	0.232	0.001	0.007	0.870
Hispanic ethnicity	0.007	0.010	0.491	0.033	0.009	<0.001
Parent education (years)	-0.057	0.013	<0.001	-0.002	0.011	0.852
Household income (ordinal)	-0.097	0.013	<0.001	0.035	0.012	0.003
General exposome adversity				0.285	0.011	<0.001
Household adversity				0.083	0.008	<0.001
Neighborhood environment				-0.021	0.009	0.024
Day-to-day experiences				0.518	0.008	<0.001
State environment				0.027	0.008	0.001
Family values				-0.019	0.008	0.018
Pregnancy/birth complications				0.014	0.008	0.075
Adjusted R^2	0.039			0.382		

Exposome factor score associations to general *P-factor* scores derived from a linear regression model.

Abbreviation: SE = standard error.

Figure 4. Association of exposome factor scores with obesity and pubertal development.



Association of the exposome factor scores with obesity (binary variable, BMI>=95th percentile, **top panel**) and late or post-pubertal status (binary variable, contrasted against pre-, early and mid-pubertal status, **bottom panel**). Odds ratios were extracted from a binary logistic regression model with exposome scores as independent variables, covarying for age, sex, race (White, Black, Other), ethnicity (Hispanic), parent education, and household income. Puberty model also co-varies for BMI.

Abbreviation: BMI = body mass index.